REMARKS

Amendment of Title

The Examiner has required that the Title be amended to describe the claimed invention. The title has been so amended to read "Imidazoles having Reduced Side Effects".

Specific Reference to Prior Applications

The Examiner requested that the first sentence following the title be amended to indicate the status of parent patent application, 09/329,752. This sentence has been amended to state that the '752 application is now abandoned.

Rejection of Claims 88-194 Pursuant to 35 USC 112(2)

The Examiner has rejected claims 88-194 as allegedly failing to define the invention. Applicant respectfully requests that the Examiner more clearly indicate which claims stand rejected on this ground; the currently pending claims are 1-108.

The Examiner has indicated that the language "and all pharmacologically acceptable . . . and racemic mixtures" must be changed to substitute the word "or" for the word "and". Applicants have made this amendment.

The Examiner has also found the terms: "esters", "condense to form", "optional double bonds", "selective agonist activity", "adrenergic receptor subtype(s)", "condense 'together to form", and "may share" indefinite. Applicants have the following comments.

The Applicants submit that the term "esters" as it appears is patentably definite Streitweiser and Heathcock, Introduction to Organic Chemistry Ch. 18, 451 (1976) defines an ester as a functional group derivative of a carboxylic acid (and convertible into a carboxylic acid by simple hydrolysis) in which the hydroxy group is replaced by an alkoxy group. Because a drug can undergo hydrolysis into the carboxylic acid form in the stomach, in the past those of skill in the pharmaceutical arts have made use of the this fact to, for example, control the stability or solubility of a drug by manufacturing and delivering the drug in the ester form. The compound of claim 1, for example, have R1, R2, and R3 groups which are capable of being carboxylic acid groups. It thus would be clear to the person of ordinary skill in the art what the meaning of the word "esters" is, and that the claim is therefore sufficiently definite so as not to negate patentability; "[i]f the claims, when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more," *Miles Laboratories, Inc. v. Shandon* 27 USPQ2d 1123, 1126 (Fed. Cir. 1993).

The language "condense to form", "condense together to form", or similar language, which appears in claims 1, 2, 9, 10, and 71, has been amended to merely state "together comprise" or similar language. This phrase thus is now sufficiently definite, and Applicants believe this ground for rejection is now overcome.

The phrase "selective agonist activity" is defined on page 6 of the patent specification as a compound which is approximately 10 times more potent as an agonist at the preferred receptor than at the non-preferred receptor. Thus, this term is submitted to be patentably definite.

Similarly, "adrenergic receptor subtype(s)" is a term which is not only well known in the art, but is explained in the specification e.g., on page 6-7 and 85 and 86. Given this, and given the context of the term in the claims, it is submitted that the term does not render the claims indefinite.

The term "may share" in claim 2, has been amended to state "optionally shares". Where there is no ambiguity as to the alternatives, the word "optionally" is not indefinite. MPEP §2173.05(i)(III) (Rev. 1, Feb. 2000). In this case, there can be no ambiguity; either the double bond is shared or it is not.

[redacted]

Similarly, the term "optional double bonds", present in claim 1 is clear; either the indicated double bonds are present or they are not.

Rejection of Claims 1-45 and 47-57 Pursuant to 35 USC §102(b)

The Examiner has rejected the above-indicated claims as allegedly anticipated over Kihara et al., Japanese Pat. No. 1/24257. Applicants respectfully traverse this rejection for the following reasons.

All claims are dependent upon claim 1. Claim 1 contains the proviso that "if the ring containing Y is a cyclohexane ring or a heterocyclic 5-member ring, said ring is not fully unsaturated".

Kihara discloses phenyl derivatives of the indicated imidazoles, and a single unsubstituted thiophene derivative thereof. The above referenced proviso thus specifically excludes from all the pending claims compounds of the structure disclosed in Kihara, since both a phenyl group and a thiophene group are fully unsaturated 6 and 5 member rings structures, respectively.

Rejection of Claims 1-106 Pursuant to 35 USC §103(a)

The Examiner has rejected claims 1-106 as allegedly obvious over Kihara et al., or Toyko (WO94-07866 or Orion (WO97-12874 or Boyd I or II or Zhang et al. Applicants assume that the Examiner meant to reject claims 1-108; all the pending claims. If this is not correct, Applicants request clarification. Applicants respectfully traverse this rejection for the following reasons.

The present invention is directed to compounds having a particular structure and which are selective agonists of the alpha 2_B and/or 2_B and 2_C adrenergic receptor subtypes. Thus, the claimed compounds are defined by structural and functional limitations, and the patentability of each of the rejected claims must be considered in light of all its limitations.

The claimed compounds have activity useful in the therapeutic treatment of numerous conditions including glaucoma, high intraocular pressure and pain without the side effects such as sedation and/or cardiovascular effects (lowered heart rate and/or blood pressure) seen with the commonly used alpha pan-agonists such as clonidine.

The Examiner has rejected the claims on the basis of structural similarities alone. The Examiner states "[t]he claimed compounds are so closely related structurally to the claimed compounds as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties. . . No showing of any unobvious or unexpected properties has been forthcoming." Office Action of September 25, 2001 at page 3. However, Applicants respectfully dispute this statement.

Contrary to the Examiner's contention, the specification clearly indicates that the claimed compounds "possess desirable therapeutic properties associated with adrenergics without having one or more undesirable side effect such as changes in blood pressure or sedation." The specification makes clear that such undesirable side effects is minimized by selecting compounds of the indicated structure which have minimal alpha 2A agonist activity which also have alpha 2B or 2B/2C agonist activity. Such a finding is clearly unexpected and non-obvious; the Examiner has not shown such a suggestion anywhere in the cited references that would motivate one of ordinary skill in the art to invent the instantly claimed compounds.

The Examiner argues that compounds of similar structure have similar activities (thus, presumably arguing that the claimed compounds are equivalent to the compounds of the prior art), but has cited no support for this statement. By contrast, the present specification provides evidence <u>on its face</u> that demonstrates that very slight changes in the structures of the indicated compounds can have drastic effects on the activity of the modified compound: compare, for example, Examples L and C-6 on page 91 (similar compounds; the latter compound has almost no alpha 2_C receptor activity, while the former compound has half maximal alpha 2_C activity); compare also Example D-1 on page 88 with Example D-2 on page 92, where the deletion of a single methyl group abrogates all alpha 2_A receptor activity detectable using the RSAT methods disclosed in the specification. Thus, the specification provides evidence that imidiazole compounds of similar structure do not necessarily have similar activities.

[redacted]

To specifically address the cited references, Kihara has been mentioned above – although Applicants have not had the entire application translated, Applicants have found no suggestion in Kihara of the specific subgenus of alpha 2 adrenergic agonist compounds claimed herein, that have the properties of reduced side sedation by virtue of their reduced ability to activate the alpha 2A receptor.

Boyd I and Boyd II are drawn to a class of thiophene derivatives of imidiazole which are said to have analgesic activity and reduced sedative side effects. However, both Boyd references appear to correlate such activity with rat alpha 2_D receptor binding ability (see, e.g., Boyd '720 at column 6, line 53, through column 7, line 17 and Table II; moreover, these references state: "[t]he activity of the compounds of the invention as analgesics may be demonstrated by the . . . in vitro assays described below: alpha 2_D adrenergic receptor binding assay. . . " E.g., *id.* at column 6, lines 49-52.) As known by those of skill in the art, the rat alpha 2_D receptor is analogous to the human alpha 2_A receptor. Thus, Boyd I and Boyd II teach away from the present invention by implying that alpha 2_A binding ability is necessary for analgesic activity, while the claimed invention is drawn to compounds which have little or no alpha 2_A activity.

Tokyo (WO94/07866) is a Japanese language reference which discloses a class of aromatase inhibitors said in the English language abstract to be useful for the treatment of estrogen-dependent cancers. The generic structure indicates that these compounds are imidazole derivatives. It is known to those of skill in the art that a compounds ability to inhibit aromatase does not depend upon binding to any alpha adrenergic receptor. There is no mention in the abstract of any of these compounds' use in the treatment of pain, their ability (or lack thereof) to bind to any alpha adrenergic receptor, or their ability to act as an analgesic with minimal cardiovascular or sedative side effects. Thus, there is nothing in this reference that would suggest the instantly claimed compounds, including all limitations of the claim, to the person of ordinary skill in the art.

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The Orion reference (WO97/12874) discloses a class of alpha 2 receptor specific compounds. However, these compounds are disclosed as being useful as "sedative and analgesic agents" page 1, line 13. The compounds' selectivity were only tested for the ability to bind unresolved alpha 2 receptors, as compared to binding affinity to unresolved alpha 1 receptors. Thus, as above, there is no suggestion of the subclass of compounds which selectively the alpha 2B or alpha 2B/2C receptor subtypes without significantly activating the alpha 2A receptor subtype, or the advantages to be obtained from such compounds. Without such suggestion, the Orion reference cannot be properly held to render the present invention obvious.

Finally, although the Examiner has not rejected any claim over the combination of any of these references, for the reasons given above no combination of these references provides a suggestion to the person of ordinary skill in the art to choose or make the compounds presently claimed. Any such combination lacks a suggestion that the side effects of sedation or cardiovascular depression are attributable to activation of the alpha 2A receptor and may be reduced by designing compounds which have a lessened ability to activate this receptor.

Provisional Double Patenting Rejection

The Examiner has provisionally rejected claims 1-106 as allegedly claiming the same invention as that of the claims of co-pending application 09/679,919 pursuant to 35 USC §101. The '919 application has since issued as US Patent 6,329,369 on December 11, 2001; thus Applicants assume this is now a non-provisional rejection. Applicants traverse this rejection for the following reasons.

As indicated in MPEP § 804, a statutory double patenting rejection is appropriate when "an invention [is] drawn to identical subject matter." *Id.* at 800-16. Thus, "[a] reliable test for double patenting under 35 USC §101 is whether a claim in the application could be literally infringed without literally infringing a corresponding claim in the patent. . . Is there an embodiment of the invention that falls within the scope of one claim, but not the other? If . . . [so], then identical subject matter is not defined by ;both claims, and statutory double patenting would not exist." *Id.*

In the present case, the claims of the '369 patent are all drawn to methods of use. The claims of the present application are all drawn to compounds. Thus, any use of the instant compounds other than those claimed in the '369 patent would not literally infringe the '369 patent. Additionally, the scope of compounds to which the methods of use is drawn is broader than the scope of the compounds of , e.g., claim 1, the broadest claim of the present application. For these reasons, there is not identical subject matter in the claims of the '369 patent and the present application, and there cannot be statutory double patenting.

CONCLUSION

For the above reasons Applicants believe the claims are now in condition for allowance, and respectfully request that the Examiner issue a Notice to that effect. No fee is thought to be required in connection with this communication. However, if Applicant is in error in this regard, please use Deposit Account 01-0885 for payment of any fee that may be due.

Respectfully Submitted,

Date: 12/20/01

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MARKED-UP VERSION OF THE AMENDMENTS

In the Title:

Kindly replace the title with the following: -- Imidiazoles Having Reduced Side Effects –

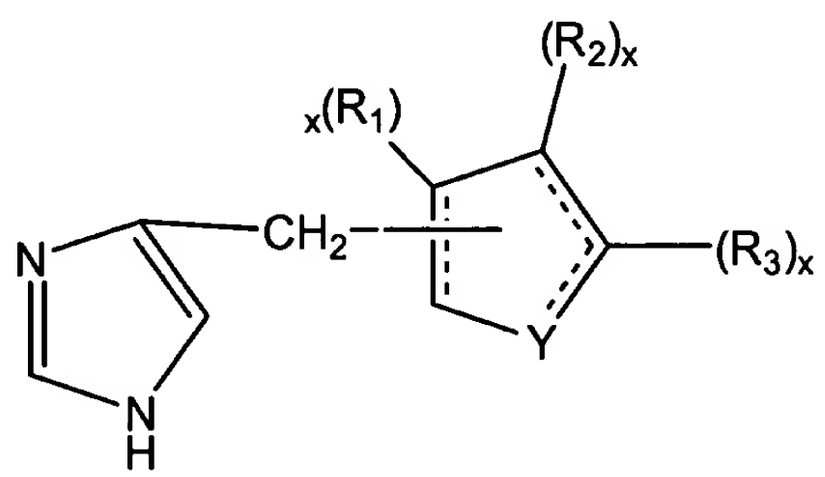
In the Specification:

Kindly amend the first sentence following the title to read as follows:

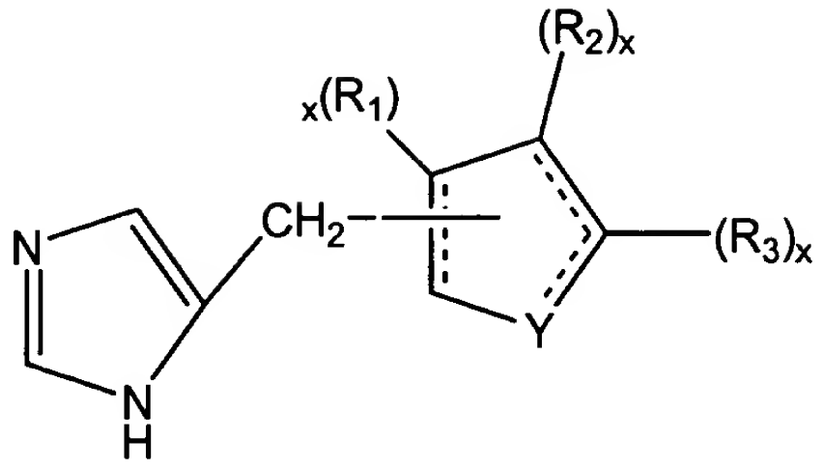
-- This application is a continuation in part of application serial number 09/329,752, filed June 10, 1999, now abandoned, which was a continuation in part of application serial number 09/205,597, filed December 4, 1998, now abandoned, which was a continuation in part of application serial number 08/985,347, filed December 4, 1997, now abandoned.—

In the Claims:

1. (Amended) A compound having a structure selected from the group consisting of:



and



in which each x is independently 1 or 2;

each R_1 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; oxo; or $-(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$ where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or H_{1-2};

each R_2 and each R_3 are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H; C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; oxo; or $-(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$ where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or H_{1-2}; or an R_2 and an R_3 together [condense to form] comprise a saturated, partly saturated, or unsaturated ring structure having the formula $-(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ $-X_t$—$(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl and oxo where each p is independently 1 or 2, q is 0-5, r is 0-5, u is 0-5; each X is independently O, S, or N and s is 0 or 1; provided that q + r + u + s + t is less than 6;

Y is selected from the group consisting of O; S; N; --$(C(R_7)_z)_s$—where each R_7 is independently as previously defined for R1, each z is independently 1-2, and s is 1-3; --CH=; --CH=CH--; or Y_1CH_2—where Y_1 is O, N, or S; and the dotted lines are optional double bonds, with the proviso that if the ring including Y is a cyclohexane ring or a heterocyclic 5 member ring said ring is not fully unsaturated, and that if Y is O, N or S, the ring including Y contains at least one said double bond,

said compound further having selective agonist activity at the α2B or α2B/α2C adrenergic receptor subtype(s) over the α2A adrenergic receptor subtype,

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and all pharmacologically acceptable salts, esters, stereoisomers [and] or racemic mixtures thereof.

2. (Amended) The compound of claim 1 in which the ring including Y has either a single double bond or no double bond, except that when an R_2 and an R_3 [condense] together [to form] comprise a saturated, unsaturated or partly saturated ring structure said Y-including ring [may] optionally shares an additional double bond with said condensed ring, provided Y is not S, O, or N.

9. (Amended) The compound of claim 2, in which each R_2 and each R_3 are independently selected from the group consisting of: H; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; halide; trihalomethyl; cycloalkyl; $(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$, where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or H_{1-2}; or an R_2 and an R_3 together [condense to form] comprise a saturated, partly saturated, or unsaturated ring structure having the formula $-(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ -X_t—$(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; and oxo where each p is independently 1 or 2, q is 0-4, r is 0-4, u is 0-4; each X is independently O, S, or N, s is 0 or 1, and q + s+ r + t + u = 3 or 4.

10. (Amended) The compound of claim 3, in which each R_2 and each R_3 are independently selected from the group consisting of: H; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; halide; trihalomethyl; cycloalkyl; $(CH_2)_n$-X-$(CH_2)_m$-$(R_5)_o$, where X is O, S or N, n is 0-3, m is 0-3, o is 0-1, and R_5 is methyl or $H_{1-2;}$ or an R_2 and an R_3 together [condense to form] comprise a saturated, partly saturated, or unsaturated ring structure having the formula $-(C(R_6)_p)_q$-X_s-$(C(R_6)_p)_r$ -X_t—$(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; and oxo where each p is independently 1

or 2, q is 0-4, r is 0-4, u is 0-4; each X is independently O, S, or N, s is 0 or 1, and q + s+ r + t + u = 3 or 4.

71. (Amended) The compound of claim 53 in which an R_2 and an R_3 together [condense to form] comprise a saturated, partly saturated, or unsaturated ring structure having the formula $-(C(R_6)_p)_q-X_s-(C(R_6)_p)_r-X_t—(C(R_6)_p)_u$ where each R_6 is independently selected from the group consisting of H; halogen; C_{1-4} alkyl; C_{1-4} alkenyl; C_{1-4} alkynyl; --COR_4 where R_4 is H, C_{1-4} alkyl or C_{1-4} alkoxy; C_{3-6} cycloalkyl; aryl; heteroaryl; cyano; nitro; trihalomethyl; and oxo where each p is independently 1 or 2, q is 0-4, r is 0-4, u is 0-4; each X is independently O, S, or N, s is 0 or 1, and q + s+ r + t + u = 3 or 4.